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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,864	03/30/2006	Wen-Luan Wendy Hsiao	32144183.4	8549

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WILKINSON & GRIST  
6TH FLOOR, PRINCE'S BUILDING  
CHATER ROAD, CENTRAL  
HONG KONG,  
CHINA

EXAMINER
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GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
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1634

MAIL DATE	DELIVERY MODE
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11/24/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/516,864	<b>Applicant(s)</b> HSIAO ET AL.	
	<b>Examiner</b> JEANINE A. GOLDBERG	<b>Art Unit</b> 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 03 September 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 30-37 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 30-37 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. This action is in response to the papers filed September 3, 2008. Currently, claims 1-4, 30-37 are pending.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 3, 2008 has been entered.
3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
4. Any objections and rejections not reiterated below are hereby withdrawn.

### ***Election/Restrictions***

5. Applicant's election with traverse of Group 1, Claims 1-29 directed to gene-encoded beta-catenin in the paper filed August 6, 2007 is acknowledged.

The response asserts that the practice regarding nucleotide sequences permits examination of up to ten sequences as set forth in the 1996 OG notice.

An OG Notice published March 27, 2007 rescinded the 1996 OG Notice that provided for a partial waiver of the requirements for restriction practice by permitting examination of a reasonable number, up to ten, independent and distinct polynucleotide molecules in a single 35 USC 111(a) or 35 USC 371 application. The Notice indicated

that the standard of independence and distinctness would be applied to polynucleotide claims filed in an application under 35 USC 111(a). Additionally, the March 27, 2007 OG Notice specifically spoke to the issue of burden of searching more than one independent and distinct invention.

Applicant was provided an opportunity to specifically state on the record that the species were not patentably distinct. "Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention." Applicants do not appear to have availed them of this opportunity.

The response asserts that election of species practice requires that the examiner must examine all members of the Markush group if the search may be made without serious burden. The response asserts that examination of a gene-encoded beta catenin; a gene-encoded alpha-catenin; and a gene encoded E-cadherin would not place undue burden upon the examiner. This argument has been reviewed but is not considered persuasive because each of these genes encode distinct proteins. Although the applicant asserts that the genes are associated, the genes would require a separate search and examination.

The requirement is still deemed proper and is therefore made FINAL.

***Priority***

6. This application is a 371 of PCT/US03/20587, filed June 27, 2003 and provisional application 60/392,191, filed June 28, 2002.

***Drawings***

7. The correction to the drawings has been reviewed. Drawing pages 4-5 have been cancelled as requested by applicant.

***Information Disclosure Statement***

8. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Pages 16-17 contains a list of references. Any references appear in the list and not listed on the IDS have not been considered.

***Claim Objections***

9. Claim 35 is objected to because of the following informalities. The claim is directed to primers "franking". The claim appears to contain a mis-spelling. The claim is presumed to mean "flanking". Appropriate correction is required.

### ***Sequence Rules***

10. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

- a. Table 1 contains 6 primers, for example, that are not identified by SEQ ID NO:. Table 3 similarly comprises primers not identified by SEQ ID NO:.  
Correction is required.

### ***Claim Rejections - 35 USC § 112- Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-4, 30-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of

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direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and breadth of claims

The claims are broadly drawn to a method for detecting colorectal carcinoma in a human patient by extracting blood serum or plasma, measuring an amount of a nucleic acid associated with encoding catenin and determining the possibility of the presence of colorectal cancer based on the amount beta-catenin nucleic acid.

The invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Adenomas are benign epithelial tumors arising in epithelium of mucosa (stomach, small intestine and bowel), glands (endocrine and exocrine) and ducts. Thus, Adenomas are not cancer.

The art (Wong et al. *Clinical Cancer Research*, Vol. 10, pages 1613-1617, March 2004) teaches the quantification of plasma b-catenin mRNA in colorectal cancer and adenoma patients. Wong teaches detecting mRNA in plasma in colorectal carcinoma, colorectal adenoma and normal subjects. The results are listed below.

Carcinoma

1480-933100

Adenoma	541-2254
Normal	0-1366

Wong teaches that b-catenin mRNA was detected in the plasma of all 58 colorectal cancer patients; 49 colorectal adenoma patients and 36 or 43 (**84%**) of normal subjects. Thus, the majority of normal patients express b-catenin mRNA in the plasma. Figure 1A illustrates the overlapping ranges of mRNA copies in plasma. Wong states that a more intensive study is necessary to explore whether plasma b-catenin mRNA concentration may be a prognostic factor. Wong further proposes that a large-scale study would be needed to investigate whether plasma b-catenin mRNA might have a role in population screening for colorectal cancer (page 1616, col. 2).

Osman et al (Clin Cancer, Res. Vol. 12, No. 11, pages 3374-3380, June 2006) teaches analysis of biomarkers in the blood for various cancers. Osman teaches testing a hypothesis that blood cell gene expression can differentiate between different cancers as well as between controls. Osman teaches concludes the gene expression patterns found in bladder cancer was distinguishable from other cancers. Thus, Osman teaches an expression pattern for one gene in the blood is not indicative of any cancer.

Fleischhacker et al. (Biochimica et Biophysica Acta, Vol. 1775, pages 181-232, 2007) provides a review of circulating nucleic acids (CNAs) and cancer. Fleischhacker teaches that contradictory results have been published between the detection of free-circulating plams mRNA and clinical data (page 214, col. 2). Fleischhacker teaches the DNA yield from serum is higher than that from plasma (page 219, col. 1).

Guidance in the Specification.

The specification teaches analysis of plasma RNA in carcinoma, adenomas and normal individuals. The results showed that 100% of patients with carcinoma, 11/14 patients with adenoma and 1/10 healthy volunteers carried b-catenin RNA (page 6, lines 19-25). The specification further teaches a quantitative analysis of plasma blood B-catenin RNA. The specification teaches the adenoma b-catenin mRNA was 30 fold higher than in normal individuals.

Carcinoma	6700-44000
Adenoma	690-1800
Normal	0-169

The specification further teaches detection of b-catenin DNA in serum of patients with colorectal adenoma and carcinoma. The specification teaches that serum B-catenin DNA is detectable in all patients with colorectal carcinoma and 9/10 patients with colorectal adenoma, while all 10 healthy individuals were free of serum b-catenin DNA (page 9, lines 12-15).

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

#### Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

The claims are directed to measuring an amount of a nucleic acid encoding catenin, namely beta-catenin nucleic acid. The skilled artisan would be unable to measure an amount of b-catenin as a positive indicator of cancer because the results illustrate overlapping ranges of cancer, adenoma and normal individuals with circulating b-catenin.

The concentration taught in the specification for carcinoma patients ranges from 6700-44000 and the range in normal patients is 0-169. The ratio of  $6700/169 = 39$  which is within the range for adenoma. This again provides results inconsistent with the claims. Therefore, the quantitative ratios provided in the claims do not appear to enable any reliable detection of carcinoma, adenoma or absence of carcinoma/adenoma. The skilled artisan would be unable to use the teachings to accurately determine the status of the patient.

Furthermore, the claims are drawn to serum or plasma levels. Fleischhacker teaches the DNA yield from serum is higher than that from plasma (page 219, col. 1). The instant specification only provides quantitative analysis for plasma. There is no indication that the serum and plasma levels are in proportion. Therefore, since the art teaches that the serum and plasma levels are expected to differ. And there are no teachings how these levels for b-catenin differ, the skilled artisan would be required to perform further experimentation which is unpredictable to determine how the ratios in the different populations range. There is no expectation that the ranges will not be overlapping, as the plasma levels are overlapping.

The claims are directed to "a nucleic acid associated with encoding catenin". The response to the restriction requirement asserts that a gene-encoded alpha-catenin; and a gene encoded E-cadherin are associated genes. The instant specification fails to provide any analysis of a gene-encoded alpha-catenin; and a gene encoded E-cadherin

and colorectal cancer or any cancer. As noted above, Osman teaches that each gene has different profiles in different cancers and thus would require analysis to confirm the pattern of the expression. The art similarly fails to provide any analysis. With regard to the quantification claims, there is no analysis of the concentration of the “associated” genes and whether the same ranges are applicable.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

#### Level of Skill in the Art

The level of skill in the art is deemed to be high.

#### Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art and the specification do not support the claims. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties in cancer diagnostics in the serum and plasma. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

#### **Response to Arguments**

The response traverses the rejection.

The response asserts that the 112 first paragraph rejection is erroneous as a matter of law because art references cannot be used unless the inventor is untrustworthy or unbelievable. This argument has been reviewed but is not persuasive. MPEP 2164 states that while a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. *Gould v. Quigg*, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. Here the teachings of Wong illustrate the unpredictability of detecting colorectal carcinoma by measuring an amount of beta-catenin. Wong demonstrates the unpredictability in the art related to the levels of B-catenin in plasma and serum as indicative of colorectal cancer. The response asserts that the statement from Wong as using plasma b-catenin RNA measurements for screening for colorectal cancer is just one statement. This argument has been reviewed, but not convincing. Wong clearly teaches the analysis, similar to the instant specification, but cautions the use of the data without additional investigations and a large scale study. It does not appear to be contrary to the entire reference as a whole because Wong while noting a potential of plasma B-catenin mRNA as a marker for colorectal cancer patients, suggests additional experimentation is needed prior to using this as a diagnostic screening, as specifically claimed in the

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instant claims. The Wong reference provides data of overlapping ranges, and data which raises the issue of unpredictability of the art and the enablement of the instant claims.

The response further asserts the 112 rejection is erroneous as a matter of fact. The response asserts the Wong reference supports the present invention. The response asserts that measuring the blood level of b-catenin is a good tool for detecting colorectal cancer. This argument has been reviewed but is not persuasive. The data provided in the chart illustrates the overlapping ranges such that colorectal cancer can not be detected by measuring the amount of b-catenin. For example, if an ordinary artisan measures an amount of 1500, the specification appears to suggest an adenoma (see page 8). Alternatively, if the artisan looks at Wong, they would be unable to determine whether it was an adenoma or carcinoma. Thus, it is unpredictable how the amount of b-catenin determine whether a patient has colorectal carcinoma.

The response filed January 15, 2008 provides a table on page 15 of the ratio range/36. it is noted that 6700/36 is not 185 as represented by the table. Similarly, 44000/36 is 1222 and not 1225. It is unclear where the numbers from the response are derived.

	USSN 10/516,864		Ratio Range / <b>(36)</b>
	Range	Median	
Carcinoma	6700-44000	22000	185-1225
Adenoma	690-1800	1100	20-50
Normal	0-169	<b>36</b>	0-5

If a similar table is constructed for the data from Wong, the ranges of ratios are overlapping.

Wong	
Range	Median
1480-933,100	8737
541-2,254	1218
0-1,366	291

Ratio Range/(291)
5-3206
1.9-7.7
0-4.69

This illustrates the overlapping ratios and ranges and provides evidence of the unpredictable results. In the event that one were to obtain a ratio of 5, looking at applicants data in the specification, the person is deemed normal. However, looking at the data from Wong, a ratio of 5 indicates both adenoma and carcinoma. It is unclear how to determine whether a person is normal or has cancer based upon such a ratio. Looking at the ratio of adenoma, the ratio from Wong is not within any of the ranges from the specification. Thus, it is unpredictable. Similar discrepancies could be noted with the ranges, medians and ratios.

The response filed June 26, 2008 asserts that one of skill in the art may decide the baseline or threshold to be set at 540, above which the measurement would indicate presence of an abnormal amount of beta-catenin mRNA and need for more invasive check for possible presence of adenoma and carcinoma. This argument has been reviewed but is deemed not persuasive. The specification provides no thresholds or baselines. The specification does not suggest further invasive checks if a particular value is found. The claims are directed to measuring an amount of nucleic acid and determining a possibility of the presence colorectal cancer. The specification does not

provide the necessary guidance for the skilled artisan to determine the possibility of the presence of colorectal cancer based upon an amount of beta catenin.

The response asserts that para 30 discusses serum analysis. This argument has been reviewed. Example 5 is directed to serum of patients with colorectal adenoma and carcinoma. The specification however fails to provide any analysis of levels, as required by claims 22. As noted by Fleischhacker, and acknowledged by the response, serum and plasma levels vary. Thus, it is unpredictable the level of the b-catenin in serum without further unpredictable and undue experimentation.

The declaration under 37 CFR 1.132 filed January 15, 2008 is insufficient to overcome the rejection of the claims based upon the unpredictability in the art as set forth in the last Office action. The declaration appears to be directed only to part of the enablement rejection to clarify the results and provide a figure illustrating the results in para 30 of the specification. The declaration further provides an explanation regarding the authorship of the Wong references, however, this does not appear to be related to the enablement rejection. Finally, the declaration states that beta-catenin is representative of many catenin/cadherins and the expression patterns would be similar. First, the additional species amended to be presented in Claim 1, for example have not been considered for the reasons above in the response to the election of species. Moreover, the arguments provided in the declaration are not in the form of evidence. With respect to the Osmer reference, the references was used to demonstrate that one gene is generally not enough for a diagnostic without further data and that each gene

has different profiles in different cancers and thus would require analysis to confirm the pattern of the expression.

With respect to Fleischhacker, the reference is used to demonstrate the differences in serum and plasma levels, thus demonstrating the unpredictability in levels and ratios between serum and plasma. The level determined for serum would not be analogous to the level of plasma. Thus, the claims specifically requiring levels and ratios are unpredictable. The response appears to agree with this analysis since the response states "plasma will yield a greater amount of RNA and DNA than serum (see page 12 of the response filed January 15, 2008).

The response asserts that no evidence has been provided to contradict the enablement. This argument has been considered but is not convincing because the teachings of Wong, Fleischhacker each suggest that b-catenin amounts would not determine or detect colorectal cancer. Moreover, it is clear that serum and plasma levels differ and as such, the ratios would be different and unpredictable.

The response, filed June 26, 2008, states that an examiner cannot simply use the teachings of the reference as the basis to reject the claimed invention as unenabled, as if the only cited reference speaks the truth. When in conflict with the claimed invention. This argument has been reviewed but is not convincing. The examiner has weighed the evidence in the specification, the state of the art, the unpredictability of the art and the evidence in the art to find that it is unpredictable to detect colorectal cancer based upon an amount of nucleic acid.

Thus for the reasons above and those already of record, the rejection is maintained.

***Conclusion***

12. No claims allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

**/Jeanine A Goldberg/  
Primary Examiner, Art Unit 1634  
November 21, 2008**